Post-licensure safety summary: Quadrivalent meningococcal conjugate vaccine (MCV4, Menactra®)

John Iskander MD MPH
Immunization Safety Office
Office of the Chief Science Officer

Outline

- Summary of Vaccine Adverse Event Reporting System (VAERS) data
- Recap of data on Guillain-Barré syndrome (GBS) following MCV4
- Update on available Vaccine Safety Datalink (VSD) data and planned/ongoing studies

Methods

- VAERS data reviewed for April 2005 through November 2006
  - Descriptive epidemiology of reports
  - Dose-adjusted reporting rates
  - Serious adverse events (SAE) as defined by Code of Federal Regulations (CFR)*
- Dose distribution data obtained from manufacturer
- VSD vaccine uptake data reviewed

*event resulted in hospitalization, death, life-threatening illness or disability; no causality implied

VAERS system description

- National passive surveillance system for vaccine adverse events

- Advantages
  - Covers US population
  - Rapidly detects signals for previously unrecognized /rare reactions
  - Generates hypothesis for pre-existing risk factors that may promote reactions
  - Permits monitoring for known reactions

- Limitations
  - Risk of underreporting or reporting bias
  - Possibly incomplete data

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Vaccine Adverse Event Reporting System (VAERS)

P.O. Box 1100

Rockville, MD 20849-1100

Toll-free 1-800-822-7967

Toll-free (fax) 1-877-721-0366

Email info@vaers.org

URL http://www.vaers.hhs.gov/

MCV4 events reported to VAERS

- 1,053 total reports; 106 (10.1%) met criteria for SAE
- 7.5 million doses distributed between April 2005-November 2006
  - Total number of doses administered overall and by age groups not available; limited published data on usage of MCV4
    - Enger KS Stokley S, J Adolesc Health 2007
- Dose-adjusted reporting rates:
  - Overall 14.0/100,000 doses
  - SAE 1.4/100,000 doses

Table 1

Demographics, seriousness of adverse events and vaccines reported after Menactra

	Non-serious (N=947)	Serious (N=106)	Total (N=1053)
Age			
2-10	29	0	29
11-17	550	72	622
18-25	321	28	349
26+	47	6	53
Sex			
Females	497	51	548
Males	444	55	499
Unknown	6	0	6
Vaccines			
Menactra alone	546	81	627
Menactra with others	401	25	426

Most frequently reported symptoms among non-serious reports

- Pain was the most frequently reported symptom (48% of reports)
- Other frequently reported adverse events included headache, fever, myalgia, vomiting, and diarrhea
- Most events (64 %) began within 24 hours after vaccination

Vasovagal syncope reports

- There were 19 reports of unintentional injury related to vasovagal syncope. Two people sustained extensive injuries:
-
  - A 17-year-old female lost consciousness, fell beneath a truck, and was burned on the muffler. She reportedly recovered
  - A 13-year-old female lost consciousness and sustained an occipital fracture and right frontal intraparenchymal bleed. She required intubation and monitoring of intracranial pressure, and follow-up information indicates that she is in rehabilitation

- In addition, two people were in motor vehicle collisions because they experienced vasovagal syncope while driving home several minutes after receiving MCV4; neither was reported to be injured

Vaccine administration errors

- Among 62 total reports:
  - 23 reports of people who received MCV4 instead of a different vaccine (most commonly pneumococcal conjugate vaccine) or MCV4 was inadvertently included among multiple vaccines to be given simultaneously to children (5 reports); no significant adverse reactions were reported
  - 13 reports that MCV4 had been given subcutaneously (SC), instead of intramuscularly (IM), with injection site inflammation as the most common sequelae
    - MMWR article in September 2006 documented additional SC instead of IM administration, with no effect on immunogenicity (www.cdc.gov/mmwr/preview/mmwrhtml/mm5537a2.htm)
  - Three reports that a patient had inadvertently received a second dose of MCV4, but no symptoms were reported
  - Four reports described errors in vaccination technique, with no adverse effects
  - Ten people over 55 years of age received MCV4; four had injection site reactions, two had rashes, one reported arthralgia in the limb in which MCV4 had been injected, and three had no symptoms.

Serious adverse events

- Total 81/106 (76%) involve MCV4 alone
- General clinical classification of reports according to organ system and type of event reported:
  (reports may receive more than one classification)

– Neurological	74
– Gastrointestinal	8
– Hematologic	8
– Dermatologic	6
– Musculoskeletal	3
– Endocrine	3
– Immunologic	3
– Cardiovascular	2
– Pregnancy related	2

Clinical classification of SAE* reported following MCV4

Event	MCV4 alone	MCV4 with other vaccines
Aseptic meningitis	5	0
Encephalitis	4	0
Seizure	2	2
Acute demyelinating encephalomyelitis (ADEM)	2	0
Transverse myelitis	2	0
Optic neuritis	2	0
Bell's palsy	2	0

*Neurological events other than GBS

Clinical classification of SAE* reported following MCV4

Event	MCV4 alone	MCV4 with other vaccines
Thrombocytopenia	5	2
Diabetes mellitus type 1	3	0
Cellulitis at injection site	1	4
Gastroenteritis	3	0
Allergic reaction	1	2

*Non-neurological events

Deaths reported following MCV4

- VAERS received two reports of death after receipt of MCV4:
- An 18-year-old male died four days after MCV4 given alone. The autopsy report listed the cause of death as presumed cardiac arrhythmia
- An 11-year-old boy developed a headache, vomiting, and abdominal pain nine days after receiving MCV4 and was hospitalized six days later. He developed encephalopathy, his neurological condition rapidly deteriorated, and he died 21 days after vaccination. The autopsy revealed acute hemorrhagic leukoencephalitis, a rare form of ADEM
-

Reports of GBS following MCV4

- Total 19 confirmed GBS cases within 6 weeks of Menactra (as of 30APR07)

- MMWR:
  - 5 cases described October 2005
  - 3 cases described April 2006
  - 9 cases described October 2006

  www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm

- Two additional cases confirmed since last MMWR

Reports of GBS following MCV4

- Ages 11-19, except for one 30-year-old male and one 43-year-old male
- Onset 2-33 days
- Six received concomitant vaccines
- Peaks observed in people who received MCV4 in summer months of 2005 and 2006
- All reported cases have recovered or are recovering

GBS after MCV4 vaccination: Rates by age

- Among 11-14 year olds in VSD
  - Expected Background rate GBS = 1.0 case/million person-months (= 4.2 cases)
  - Observed in VAERS= 1 case
  - Observed/expected ratio= 1.0 / 4.2
  - Rate ratio = 0.25 (.01 – 1.20) – Controlling for Season
- Among 15-19 year olds in VSD
  - Expected background rate GBS =1.2 case/million person-months (= 6.5 cases)
  - Observed in VAERS = 16 cases
  - Observed/expected ratio = 16/6.5
  - Rate ratio = 2.48 (1.30 – 4.55) – Controlling for Season

GBS after MCV4 vaccination: Data from VSD

- VSD Rapid Cycle Project from April 2005 through January 2007:
  - 142,816 doses administered
  - Zero cases GBS observed among vaccine recipients 11–19 years old within 6 weeks of vaccination
  - 0-1 cases were expected
- Within the VSD ~94% of MCV4 recipients are 11–19 year olds

Ongoing and proposed studies of GBS after MCV4

- Harvard Pilgrim: manufacturer-sponsored study proposes to include 10 million people 11-18 years old; would cover 42-month period from March 2005 to August 2008; would have 89% power to detect a risk ratio of 3 and 50% power to detect a risk ratio of 2
- The Clinical Immunization Safety Assessment Network, in collaboration with CDC, continues to conduct detailed clinical review and focused laboratory evaluation (when specimens are available) of GBS cases after MCV4
  - Host risk factors (i.e. genetic) also a focus for research

GBS after MCV4 vaccination: Discussion

- For 11-19 Year Olds, there is no statistically significant evidence of an increased risk of GBS after MCV4 vaccination.
- Although there appears to be an increased risk for GBS after MCV4 vaccination in the 15-19 year old age category, the inherent limitations of VAERS require that these findings be viewed with caution
- Substantial uncertainty exists regarding the risk estimate, using the VSD background incidence rate
- Timing of neurologic symptoms within 1–5 weeks of vaccination among reported cases is of concern

Summary and discussion

- Overall and SAE reporting rates within average ranges for VAERS
- Most reported events non serious and consistent with pre-licensure safety parameters
- Potentially preventable events (post-vaccination syncope and administration errors) have been detected for MCV4 and other newly licensed adolescent vaccines

Summary and discussion

- Although there appears to be a small increased risk for GBS after MCV4 in the 15-19 year old age category, these findings should be viewed with caution

- Among other SAE reported following MCV4, specific neurological and non-neurological diagnoses have been reported in relatively small numbers; their causal relationship to vaccination is uncertain

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Vaccine Uptake Data

- PURPOSE: To describe the uptake of meningococcal conjugate vaccine (MCV4) in Michigan adolescents following its approval in January 2005, and compare it to the use of meningococcal polysaccharide vaccine (MPSV4) in 2004

- METHODS: All available records of meningococcal immunizations given between February 1986 and March 2006 were obtained from the Michigan Childhood Immunization Registry (MCIR), which is used by about 95% of Michigan immunization providers. During late 2005 and early 2006, these records were analyzed by immunization type, administration date, recipient age, and health care provider type (public or private)

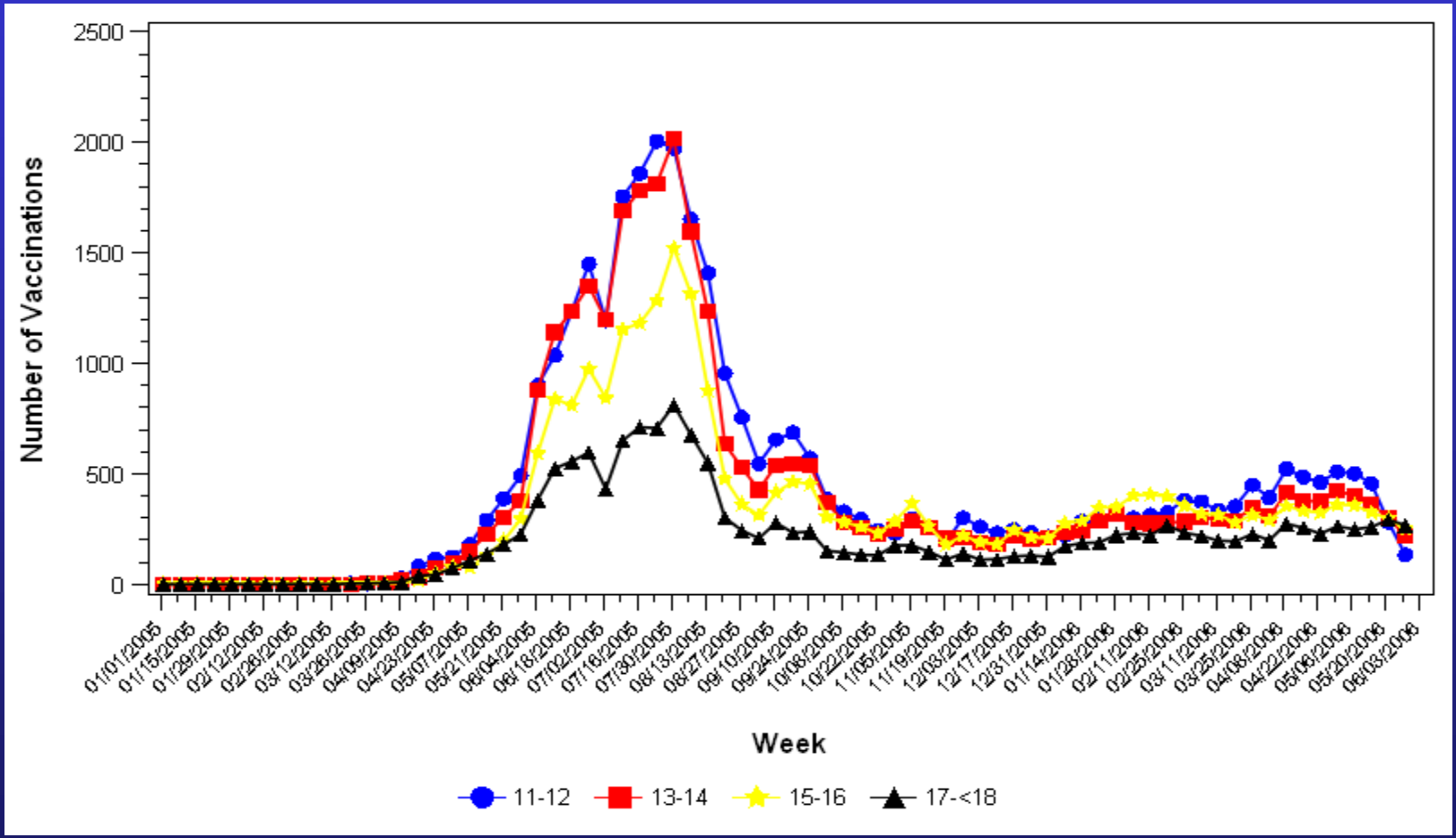
Vaccine Uptake Data (cont)

- RESULTS: The MCIR contained 63,253 meningococcal immunizations. A total of 15.2% were given in 2004, 68.8% in 2005, and 10.8% in 2006. In those years, most immunizations occurred in June, July, and August. In 2005, 85.2% were MCV4. In 2004, 17 to 18-year olds received nearly all meningococcal immunizations; in 2005, 11 to 16-year olds received 58.0% of them. Estimates of immunization coverage were 4.0% for 11 to 12-year olds, 3.4% for 13 to 16-year olds, 5.9% for 17 to 19-year olds, and 19% for freshmen entering college

- CONCLUSIONS: Compared to 2004, in 2005 there was a large increase in the number of doses administered, with more MCV4 than MPSV4. Patterns of immunization were consistent with the Advisory Committee on Immunization Practices (ACIP) recommendations. Coverage of Michigan adolescents is low, but increased in 2005 compared with 2004

Age Cohorts by MCV4 Vaccination Date for VSD Sites: Jan 1, 2005 - Apr 8, 2006

11 to 17-yos, 8 sites



Number of GBS Reports to VAERS within 6 weeks of MCV4 Administration, by Age